



NTP
National Toxicology Program

**Toxicology and Carcinogenesis Studies of
N,N-Diethylamine in F344/N Rats and B6C3F1 Mice
(Inhalation Studies)**

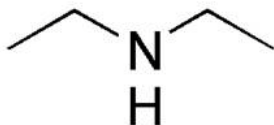
Daniel Morgan PhD, DABT
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors
Technical Reports Subcommittee
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Diethylamine



- Nomination: NIEHS, 1999
 - Chronic toxicity and carcinogenicity by inhalation
- Rationale:
 - High production volume – 25 M pounds (1995)
 - ~28,000 US workers potentially exposed
 - Lack of chronic toxicity and carcinogenicity data



Diethylamine: Use as Chemical Intermediate

- Corrosion inhibitor - N,N-diethylethanolamine (~55%)
- Pesticides, insect repellents (~20%)
- Rubber processing (~10%)
- Pharmaceuticals (<15%)
 - Disulfuram, diazepam, lidocaine, etc.
- Paints, varnishes (<15%)



Diethylamine: Studies Conducted

- Genetic Toxicity
 - Bacterial mutagenicity test
 - Mouse micronucleus assay
- 2-Week Pre-chronic Inhalation
- 3-Month Pre-chronic Inhalation
 - Clinical pathology
 - SMVCE
- 2-Year Chronic Toxicity & Carcinogenicity by Inhalation



Genetic Toxicity

- Negative in 2 bacterial mutagenicity assays +/- metabolic activation:

Salmonella typhymurium – strains: TA100, TA1535, TA1537, TA98

Escherichia coli strain: WP2 uvrA pKM101

- No increase in micronucleated erythrocytes

Male or female B6C3F1 mice, 3-mo study

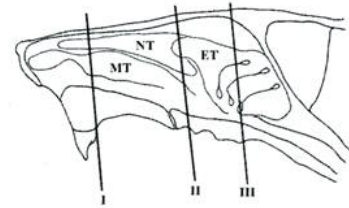


Prechronic Inhalation Toxicity of Diethylamine

Spectrum of Nasal Cavity Lesions in Rodents

- Nasal Cavity, Level I
 - Turbinate necrosis
 - Suppurative inflammation
 - Respiratory Epithelium; necrosis, hyperplasia; squamous metaplasia

- Nasal cavity, Level II
 - Olfactory Epithelium; atrophy, respiratory metaplasia
 - Respiratory Epithelium; hyaline degeneration





Results of 2-Week Studies in F344 Rats

Diethylamine (ppm):	Body Weights (% control)					
	0	31	62.5	125	250	500
males	100	99	99	91	74	59
females	100	99	101	96	82	69

Nasal Lesions (males and females)

250 & 500 ppm - moderate to marked severity

125 ppm - minimal to mild severity

Concentrations selected for 3-mo study: 0, 8, 16, 31, 62.5, 125 ppm



Results of 3-Month Studies in F344 Rats

Exposure Concentrations: 0, 8, 16, 31, 62.5, 125 ppm

- No mortality
- No effects on body weights
- No exposure related changes in clinical pathology
- Minimal - mild nasal lesions at 62.5 & 125 ppm

Concentrations selected for 2-year study: 0, 31, 62.5, 125 ppm



Reproductive Parameters in F344 Rats - SMVCE

Exposure Concentrations: 0, 31, 62.5, 125 ppm

- Concentration-related decrease in sperm motility
- No effect on estrous cycle



Results of Chronic Studies in F344 Rats

Exposure concentrations: 0, 31, 62.5, 125 ppm

- No effect on survival
- Decreased body weights in 125 ppm male and female (~11%)
- No treatment-related neoplastic lesions



Selected Nonneoplastic Nasal Lesions in Male Rats

Diethylamine (ppm)	0	31	62.5	125
Olfactory epithelium				
atrophy	2	49	50	50
hyaline droplet accumulation	8	49	49	42
hyperplasia, basal cell	0	0	22	50
Respiratory epithelium				
ulcer	0	0	2	22
hyaline droplet accumulation	0	29	42	11
hyperplasia	5	34	35	47
squamous metaplasia	0	2	6	26



Selected Nonneoplastic Nasal Lesions in Female Rats

Diethylamine (ppm)	0	31	62.5	125
Olfactory epithelium				
atrophy	1	47	48	50
hyaline droplet accumulation	11	49	50	48
hyperplasia, basal cell	0	3	29	48
respiratory metaplasia	3	1	2	19
Respiratory epithelium				
ulcer	0	0	0	34
hyaline droplet accumulation	4	48	46	39
hyperplasia	7	31	41	50
squamous metaplasia	1	1	5	39



Nonneoplastic Lesions: Eye

Cornea, inflammation, suppurative

Diethylamine (ppm)	0	31	62.5	125
male rats	0	0	1 [2.0] ^a	5 [2.4]
female rats	0	2 [2.5]	2 [2.5]	1 [3.0]

^a Average severity grade of lesions in affected animals: 1=minimal, 2=mild, 3=moderate, 4=marked



Conclusions

- **No evidence of carcinogenicity in male rats**
- **No evidence of carcinogenicity in female rats**
- **Nonneoplastic lesions:**
 - Nasal cavity - male and female rats
 - Pleura and lung - female rats



Results of 2- Week Studies in B6C3F1 Mice

Diethylamine (ppm):	Body Weights (% control)					
	0	31	62.5	125	250	500
males	100	94	97	87	73	59
females	100	101	102	91	81	68

Mortality: 2/5 males, 3/5 females at 500 ppm

Nasal Lesions (males and females)

250 & 500 ppm - moderate to marked severity

Concentrations selected for 3-mo study: 0, 8, 16, 31, 62.5, 125 ppm



Results of 3-Month Studies In B6C3F1 Mice

Exposure Concentrations: 0, 8, 16, 31, 62, 125 ppm

- No mortality
- Body weights decreased at 125 ppm - ♂ (22%) & ♀ (16%)
- No treatment-related changes in hematology
- Mild - moderate nasal lesions at 125 ppm

Concentrations selected for 2-yr study: 0, 16, 31, 62 ppm



Reproductive Toxicity in B6C3F1 Mice - SMVCE

Exposure Concentrations: 0, 31, 62, 125 ppm

- Concentration-related decrease in sperm motility
- No effect on estrous cycle



Chronic Studies in B6C3F1 Mice

Exposure Concentrations: 0, 16, 31, 62.5 ppm

- No treatment-related effects on survival
- No treatment-related effects on body weights
- No treatment-related increase in neoplasms



Nonneoplastic Lesions in Male Mice: Nasal Cavity

Diethylamine (ppm)	0	16	31	62.5
Olfactory epithelium				
atrophy	9	19	50	50
respiratory metaplasia	14	15	44	50
Respiratory epithelium				
necrosis	2	3	3	8
hyaline droplet accumulation	11	6	19	30
squamous metaplasia	4	7	16	34



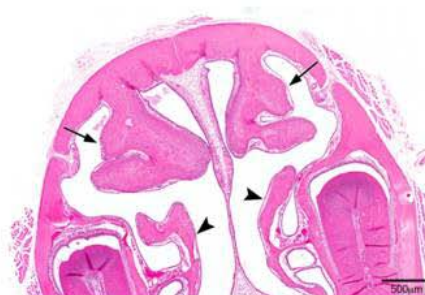
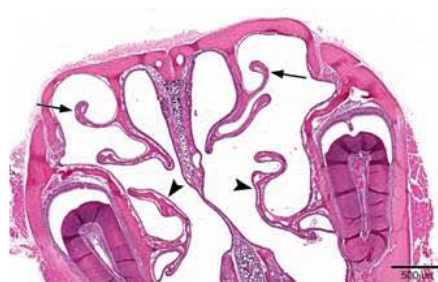
Nonneoplastic Lesions in Female Mice: Nasal Cavity

Diethylamine (ppm)	0	16	31	62.5
Olfactory epithelium				
atrophy	8	29	49	50
respiratory metaplasia	4	15	48	50
Respiratory epithelium				
necrosis	1	0	6	16
hyaline droplet accumulation	20	33	47	29
squamous metaplasia	0	0	13	35



Nasal Turbinate Hyperostosis in Mice

Diethylamine (ppm)	0	16	31	62.5
Males	5	23	50	50
Females	4	23	49	50





Conclusions

- **No evidence of carcinogenicity in male mice**
- **No evidence of carcinogenicity in female mice**
- **Nonneoplastic lesions:**
 - Nasal cavity (including hyperostosis) - male and female mice



Overall Evidence of Diethylamine Carcinogenicity

- No evidence - male rats
- No evidence - female rats
- No evidence - male mice
- No evidence - female mice